UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

WARNER CHILCOTT COMPANY, LLC, Plaintiff(s), v. LUPIN LTD, et al. Defendant(s).	:	Civil Action No. 11-5048 (JAP)
WARNER CHILCOTT COMPANY, LLC, Plaintiff(s), v. AMNEAL PHARMACEUTICALS, LLC et al., Defendant(s).	:	Civil Action No. 12-2928 (JAP) **OPINION**

PISANO, District Judge.

I. INTRODUCTION

These are patent infringement actions brought by plaintiff Warner Chilcott Company, LLC against defendants Lupin Ltd, Lupin Pharmaceuticals, Inc., Amneal Pharmaceuticals, LLC, Amneal Pharmaceuticals of NY, LLC, Inc. with respect to U.S. Patent No. 7,704,984 ("the '984 patent"). A seven-day bench trial was held during the period of October 7 through October 17, 2013, and the issue for trial was defendants' assertion that the '984 patent was

invalid based on obviousness. This Opinion constitutes the Court's findings of fact and conclusions of law. After careful consideration of the evidence before it, the Court finds in favor of Plaintiffs.

II. BACKGROUND

A. The Parties and the Nature of the Case

These are actions for patent infringement under 35 U.S.C. § 271(e)(2)(A). Plaintiff Warner Chilcott Company, LLC ("Warner" or "Plaintiff") is a limited liability company organized and existing under the laws of Puerto Rico. Final Pretrial Order ("FPO") at 4. Warner is the holder of New Drug Application ("NDA") No. 22-501, for Lo Loestrin Fe (referred to herein as "Lo Loestrin"), an oral female contraceptive product.

Defendant Lupin Limited is a corporation organized and existing under the laws of India. *Id.* Defendant Lupin Pharmaceuticals, Inc. is a wholly-owned subsidiary of Lupin Ltd., and is a corporation organized and existing under the laws of the State of Virginia. *Id.* Lupin Ltd. and Lupin Pharmaceuticals, Inc. (collectively, "Lupin") filed an Abbreviated New Drug Application ("ANDA") No. 20-3113 with the U.S. Food and Drug Administration ("FDA") seeking approval to market a product that is the subject of Lupin's ANDA, which Lupin contends is bioequivalent to, and refers to, Warner's Lo Loestrin. Pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), Lupin's ANDA certified to the FDA that the '984 patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of Lupin's ANDA Product. FPO at 5. Pursuant to 21 U.S.C. § 355(j)(2)(B), in a letter dated July 19, 2011, Lupin notified Warner that Lupin had filed its ANDA, which included a Paragraph IV Certification with respect to the '984 patent. *Id.*

On September 1, 2011, Warner filed a complaint against Lupin alleging that the filing of Lupin's ANDA infringed the'984 patent under 35 U.S.C. § 271(e)(2)(A). Lupin has since stipulated that the manufacture, use, offer for sale or sale of Lupin's ANDA product within the United States or importation of Lupin's ANDA product into the United States would infringe claims 1-9 of the '984 patent, assuming the claims are not invalid and are enforceable. *Id.* at p. 6. Lupin has asserted counterclaims against Warner alleging that the '984 patent, including all of its claims, are invalid. *Id.*

Amneal Pharmaceuticals of NY, LLC, Inc. and its parent Amneal Pharmaceuticals, LLC (collectively "Amneal") are also defendants in this matter. By Stipulation and Order dated October 7, 2013, Amneal was substituted as a defendant in Civil Action 12-2928 for Watson Laboratories, Inc. ("Watson"). Civ. Action No. 12-2928, D.E. No. 79. Watson had filed an ANDA (No. 20-2982) with the FDA, seeking approval to market a product ("Watson's ANDA Product") that Watson contended is bioequivalent to, and refers to, Lo Loestrin. FPO at 6. Pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), Watson's ANDA certified to the FDA that the '984 patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of Watson's ANDA Product. *Id.* Pursuant to 21 U.S.C. § 355(j)(2)(B), in a letter dated April 4, 2012, Watson notified Warner that Watson had filed its ANDA, which included a Paragraph IV Certification with respect to the '984 patent. *Id.* On May 16, 2012, Warner filed the instant action against Watson.

On or about October 1, 2013, Watson sold the ANDA for the Watson ANDA Product to Amneal. *Id.* Amneal has stipulated that it stands in the shoes of Watson for purposes of this litigation. Civ. Action No. 12-02928, D.E. No. 79. Further, Amneal has adopted "everything that Lupin has done through the trial as if Amneal had presented that evidence"

and agreed that "whatever decision comes down in the Lupin case with respect to the validity of the patent-in-suit … will also be entered in the Amneal suit with Warner Chilcott." Tr. 994:14–22.

B. The '984 Patent

The '984 patent, entitled "Extended Estrogen Dosing Contraceptive Regimen" was issued by the United States Patent and Trademark Office on April 27, 2010. FPO at 7-8. The 11/112,290 application that led to the '984 patent was filed on April 22, 2005. *Id.* at 8. Roger M. Boissonneault is the named inventor of the '984 patent. *Id.*

The '984 patent is directed to a method of contraception with three compositions for administration:

• the first composition containing a progestin and ethinyl estradiol;

• the second composition containing only ethinyl estradiol; and

• a final composition containing no active ingredient (progestin or estrogen), but optionally containing an iron supplement.

JTX-1 at col. 2, ll.33−46, col. 3, ll.56−63.

The nine claims of the '984 patent read as follows:

> 1. A method of contraception comprising the steps of sequentially administering to a female of child-bearing age: (a) a first composition containing a progestin in an amount equivalent to about 0.3 to about 1.5 mg norethindrone acetate wherein the progestin is selected from norethindrone acetate or norethindrone and 5 to 15 μg of ethinyl estradiol for 24 days; (b) a second composition containing 5 to 15 μg of ethinyl estradiol and substantially free of a progestin for 2 days; and (c) a third composition that is a placebo,

wherein the sequential administration of the first composition, the second composition and the third composition, is performed on a daily basis over a 28 day cycle.

2. The method according to claim 1, wherein the sequential administration is repeated beginning the day after completion of the 28 day cycle.

3. The method according to claim 1, wherein the progestin in the first composition is norethindrone acetate.

4. The method according to claim 3, wherein the amount of norethindrone acetate in the first composition is about 1 mg.

5. The method according to claim 1, wherein the placebo contains about 75 mg of ferrous fumarate.

6. The method according to claim 4, wherein the amount of ethinyl estradiol in the first and second composition is the same.[1]

7. A method of contraception comprising the steps of sequentially administering to a female of child-bearing age: (a) a first composition containing about 0.3 to about 1.5 mg norethindrone acetate and 5 to 15 μg ethinyl estradiol for 24 days; (b) a second composition containing 5 to 15 μg of ethinyl estradiol and substantially free of progestin for 2 days; (c) a third composition that is a placebo for 2 days, wherein the sequential administration of the first composition, the second composition and the third composition is performed on a daily basis over a 28 day cycle.

[1] As Plaintiff's points out, claim 6 is the narrowest of the claims and if claim 6 is invalid then the patent's other claims are invalid as well.

8. The method according to claim 7, wherein the first composition contains about 1 mg of norethindrone acetate.

9. The method according to claim 7, wherein the amount of ethinyl estradiol in the first and second composition is the same.

Id. at col. 6, ll. 23-64. All nine claims are asserted in this case.

C. Lo Losestrin Fe

Lo Loestrin is an embodiment of the '984 patent, and the '984 patent is listed in FDA's Orange Book as a patent covering the use of Lo Loestrin. DTX-335. As noted above, Warner is the holder of the NDA for Lo Loestrin, which contains the active ingredients norethindrone acetate (also referred to herein as "NA") and ethinyl estradiol (also referred to herein as "EE"). Lo Loestrin was approved by the FDA on October 21, 2010, and is indicated for use by women to prevent pregnancy. FPO at 8. Lo Loestrin is sold as a 28-day oral contraceptive regimen which includes administering on a daily basis over a 28 day cycle (i) 24 active tablets comprising 1 mg norethindrone acetate and 10 micrograms (μg) ethinyl estradiol, followed by (ii) 2 active tablets comprising 10 μg ethinyl estradiol, followed by (iii) 2 nonhormonal placebo tablets containing 75 mg ferrous fumarate that do not serve any contraceptive purpose. *Id.*

D. Witnesses at Trial

Defendants presented expert testimony from Dr. Kurt Barnhart, Dr. Jesse David, and Dr. David Blackburn. Plaintiff responded with expert testimony from Dr. Philip Darney, Dr. Risa Kagan, Dr. Ronald Thisted, and Mr. Raymond Sims. The parties also submitted testimony from Roger Boissoneault, Herman Ellman, and Hiran Patel via video deposition testimony.

Kurt T. Barnhart, M.D.

The Court recognized Dr. Barnhart as an expert in the fields of obstetrics and gynecology and clinical epidemiology and biostatistics. Tr. 55:5–10. Dr. Barnhart is a Professor at the University of Pennsylvania. He holds an M.D. from the Mt. Sinai School of Medicine. Dr. Barnhart opined that the invention claimed in the '984 patent was obvious.

Jesse David, Ph.D.

The Court recognized Dr. David as an expert in economics and the economic issues associated with patents. Tr. 254:18–23. Dr. David is a member of Edgeworth Economics. Tr. 252:1–18. He opined that the commercial success of Lo Loestrin is not probative of nonobviousness.

David Blackburn, Ph.D.

The Court recognized Dr. Blackburn as an expert in the field of economics and intellectual property issues relating to economics. Tr. 379:16–21. Dr. Blackburn is a Vice-President at NERA, an economic consulting firm. DTX-256. He opined that the commercial success of Lo Loestrin is not related to the invention claimed in the '984 patent.

Philip A. Darney, M.D., Ms.C.

The Court recognized Dr. Darney as an expert in gynecology, family planning, and contraception. Tr. 613:5–11. Dr. Darney is a Professor in the Department of Obstetrics, Gynecology, and Reproductive Sciences at the University of California, San Francisco. He is the Director of the Bixby Center for Reproductive Health at UCSF and is the Chief of the Department of Obstetrics, Gynecology and Reproductive Services at San Francisco General Hospital. FPO at 26; PTX-130A. Dr. Darney testified regarding the nonobviousness of the '984 patent.

Risa Kagan, M.D.

The Court recognized Dr. Kagan as an expert regarding clinical aspects of gynecologic practice and contraception management. Tr. 971:22–972:1. Dr. Kagan is a Clinical Professor for the University of California, San Francisco and a member of the East Bay Physicians Medical Group, an OB/GYN practice in the Bay area. PTX-128; Tr. 968:4–969:23. Dr. Kagan testified with respect to how clinicians select which oral contraceptive to prescribe, and about her clinical experience with Lo Loestrin.

Ronald A. Thisted, Ph.D.

The Court recognized Dr. Thisted as an expert in statistical methods used in the fields of medicine, biology, and pharmaceutical science. Tr. 487:19–25. 34. Dr. Thisted holds a Ph.D. in Statistics from Stanford University and is a Professor in the Department of Health Studies at the University of Chicago. PTX-129. Dr. Thisted performed statistical analyses related to the Pearl Index calculations for Lo Loestrin and Loestrin 24 Fe ("Loestrin 24"). He also performed calculations related to the number of regimens encompassed by certain prior art patents.

Raymond Sims

The Court recognized Mr. Sims as an expert in intellectual property research and analysis regarding whether a patented product is a commercial success. Tr. 320:9–15. Mr. Sims is a Vice President at Charles River Associates, an international business and economic consulting firm. He testified regarding the commercial success of Lo Loestrin.

Roger Boissonneault

Roger Boissonneault is the inventor of the '984 patent. He is the President and CEO of Warner Chilcott. FPO at 18. His testimony was submitted by way of video deposition testimony.

Herman Ellman, M.D.

Dr. Ellman is the Senior Vice President for Clinical Development of Warner Chilcott. He oversaw the clinical trials leading to the approval of Lo Loestrin. FPO at 18. His testimony was submitted by way of video deposition testimony.

Hiran Patel

Mr. Patel is a research fellow at Watson whose primary responsibility is product development. Tr. 532:20–23. Mr. Patel was Watson's Rule 30(b)(6) designee on the research and development for Watson's Lo Loestrin ANDA product. Tr. 533:17–23. His testimony was submitted by way of video deposition testimony.

E. Combination Oral Contraceptives Generally

Testimony from the parties' experts provided a comprehensive background on oral contraceptives generally. Most oral contraceptives on the market are what are referred to as "combination" oral contraceptives, meaning that they contain both an estrogen and a progestin. Combination oral contraceptives administer an estrogen and a progestin for a period of consecutive days, which are then typically followed by a hormone-free interval ("HFI") to allow for withdrawal bleeding to occur. Tr. 643:11–16. This regimen is repeated by women on the contraceptive for as long as they remain on the contraceptive. Tr. 107:4–6, 16–22. So, for example, a woman on a 21/7 regimen (*i.e.*, 21 days of the administration of hormones followed by a seven-day HFI) who completes the 28–day regimen would then

immediately start the next 28–day cycle, starting with day 1 of the new pill-taking cycle the next day.

Both Dr. Barnhart and Dr. Darney testified at trial about how combination oral contraceptives prevent pregnancy. Combination oral contraceptives prevent pregnancy primarily by inhibiting ovulation, *i.e.*, by preventing a woman from producing an egg. Tr. 632:12–20. Without an egg for sperm to fertilize, pregnancy cannot occur. Combination oral contraceptives prevent ovulation in part by stopping follicles, *i.e.*, the collections of cells in the ovaries that contain an egg, in the ovaries from developing. Tr. 69:22–25, 70:1–14. At a certain point in the menstrual cycle, these follicles grow and mature until one follicle becomes "dominant" and eventually releases the egg. Tr. 69:22–70:10; Tr. 627:4–11. But if follicles do not develop, they cannot grow big enough to reach dominance and cannot release an egg. Tr. 77:17–24; Tr. 627:4–11.

Both the estrogen and progestin component play a role in inhibiting ovulation. Estrogen does so by stopping the release of "follicle-stimulating hormone," which is the hormone released from the pituitary in the brain that causes the follicles in the ovaries to grow. Tr. 630:13–17. In the absence of sufficient amounts of follicle-stimulating hormone, follicles cannot reach a sufficient size to produce an egg.

Progestins also help inhibit ovulation. Like estrogens, progestins also help to inhibit the release of follicle-stimulating hormone, as there is better suppression of follicle-stimulating hormone when a progestin is given in combination with estrogen than when estrogen is given alone. Tr. 83:9–14. Progestins also inhibit ovulation by acting on the pituitary to stop the release of "luteinizing hormone." Tr. 630:5–14, 18–25; 631:19–20. Luteinizing hormone triggers the release of the egg from the follicle once it has developed and

become dominant. Tr. 630:21–25. In the absence of luteinizing hormone, the egg will not be released even if the follicle has otherwise sufficiently developed. Tr. 630:21–25.

Progestin and estrogen work together to inhibit ovulation by acting on the hypothalamus and pituitary in the brain to stop the release of hormones that would otherwise bring about ovulation. Tr. 630:5–631:4. According to Plaintiff's expert, these effects are dose-related. Tr. 630:5–631:2. When the levels of estrogen and progestin are too low, they will be insufficient to suppress the signals that cause ovulation, undermining the efficacy of the oral contraceptive. Tr. 693:9–17.

Combination oral contraceptives also work to prevent pregnancy through secondary "local" effects: The progestin can thicken cervical mucus (thereby impeding sperm penetration) and alter the lining of the uterus, called the endometrium (thereby making implantation of a fertilized egg in the womb less likely). Tr. 631:10–23. However, estrogen can have an "antagonistic" effect with respect to these secondary effects, because it can counteract the local effects of the progestin. Tr. 635:7–17.

Evidence showed that, consequently, there are a number of variables to be considered in determining the overall composition of an oral contraceptive. Tr. 642:6–644:7. These include (1) estrogen type; (2) estrogen dose; (3) progestin type; (4) progestin dose; (5) length of the hormone-free interval; (6) length of the regimen; and (7) order of administration of tablets. Tr. 642:6–644:7; PTX-135, at 3. Each of these are discussed in turn below:

Estrogen type: Multiple types of estrogen can be employed in a combination oral contraceptive, though most employ the synthetic estrogen EE. Tr. 642:6–10, 19–21; PTX-135. In addition to EE, the prior art described use of natural estrogens, which have different

properties than EE, and can be used in much higher doses without causing serious side effects such as deep vein thrombosis. Tr. 841:10–18, 843:8–23.

Estrogen dose: Estrogen dosage has implications for not only the efficacy, but also the safety and tolerability of the regimen. Estrogen acts synergistically with progestin in inhibiting ovulation, and is critical in preventing unscheduled vaginal bleeding. Tr. 633:5–634:1, 634:9–25. An estrogen dose that is too high poses an unacceptably high risk of deep vein thrombosis, and can also cause less serious side effects such as nausea and breast tenderness. Tr. 673:2–8; Tr. 985:3– 14, 979:12–14. An estrogen dose that is too low can undermine contraceptive efficacy by failing to inhibit follicular development and ovulation, and can undermine the side effect profile by being insufficient to prevent a high incidence of unscheduled bleeding. Tr. 673:25–678:12; 697:16–703:13; Tr. 157:11–24, 151:14–19.

Progestin type: Progestins have different pharmacologic effects, different half-lives, and different potencies that affect the tolerability and efficacy profile of a given regimen. *See* Tr. 650:21–651:25; 652:1–3.

Progestin dosage: If progestin doses that are too low, the oral contraceptive will not suppress the hormones that cause ovulation, undermining contraceptive efficacy. Tr. 692:16–693:17. Progestin doses that are too high can cause adverse effects in the liver and other parts of the body. Tr. 661:4– 662:12.

Length of HFI: At the relevant time, April 2005, the majority of marketed oral contraceptive products were “21/7” regimens, providing 21 days of combination tablets

(estrogen and progestin), followed by seven days of placebo tablets containing no hormones, for a 21/7 regimen. PTX-135.[2]

Length of regimen: Evidence showed that while most combination oral contraceptives were provided in a 28–day regimen, it is not disputed that oral contraceptive regimens need not be that length, and regimens of other lengths were known in the art. One prior art regimen called Seasonale, for example, was a 91–day regimen, providing 84 consecutive days of combination tablets, followed by seven days of placebo tablets. PTX- 135. Regimens including, for example, 24 days of combination pills were also known. *See, e.g.*, JTX 010; Tr. 126:2-136:17.

Order of administration: Consideration is also given to the order of administration of the combination tablets in relation to other tablets, such as placebo or estrogen-only tablets. Tr. 642:6–13, 643:25–644:6.

III. ANALYSIS

A. The Law of Obviousness

1. Burden of Proof

The Court's analysis starts from the presumption that the '984 patent is valid, as every claim of an issued patent is independently presumed valid. *See* 35 U.S.C. § 282. As such, a party challenging the validity of a patent claim must prove invalidity by clear and convincing evidence, and the burden of proof always remains with the challenger. *See id.*; *Microsoft Corp. v. i4i Ltd. Partnership*, 131 S.Ct. 2238, 2243, 180 L.Ed.2d 131 (2011); *Innovative Scuba Concepts, Inc. v. Feder Indus., Inc.*, 26 F.3d 1112, 1115 (Fed. Cir. 1994). Clear and

[2] An example of a contraceptive that did not follow this regimen was the contraceptive Mircette, which provided 21 days of combination ethinyl estradiol and progestin tablets, followed by two days of placebo tablets, followed by five days of tablets containing only EE, for a "21/2/5" administration scheme. PTX-135; Tr. 739:23–741:6.

convincing evidence is a higher burden of proof than preponderance of the evidence. *See Colorado v. New Mexico*, 467 U.S. 310, 316, 104 S.Ct. 2433, 81 L.Ed.2d 247 (1984). It is evidence that places in the mind of the finder of fact an abiding conviction that the truth of the factual contentions is highly probable. *See id.* Clear and convincing evidence should "instantly tilt[ ] the evidentiary scales" in favor of its proponent when weighed against the opposing evidence. *Id.*

2. Legal Standard

"A patent may not be obtained ... if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). "The [obviousness] analysis is objective" and judged as of the "time the invention was made." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406, 127 S.Ct. 1727, 167 L.Ed.2d 705 (2007) (citation omitted).

The ultimate determination of obviousness is a question of law based on underlying factual findings, including the level of ordinary skill in the pertinent art; the scope and content of the prior art; the differences between the claimed invention and the prior art; and objective indicia of nonobviousness, *i.e.*, evidence of factors such as whether the claimed invention is a commercial success, provides unexpected benefits, satisfies a long-felt need, or succeeds where others have failed. *See id.*; *see also Graham v. John Deere Co.*, 383 U.S. 1, 17–18, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966) ("[Obviousness] lends itself to several basic factual inquiries. Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or

nonobviousness of the subject matter is determined."). While party defending a patent may offer evidence of secondary considerations of nonobviousness, secondary considerations of nonobviousness may not overcome a strong prima facie case of obviousness. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed.Cir. 2010).

"[T]he results of ordinary innovation are not the subject of exclusive rights under the patent laws." *KSR*, 550 U.S. at 427. Where the issue of obviousness is based on a combination of elements found in the prior art, "the combination must do more than yield a predictable result." *Id.* at 416. In fact, "a combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* This is because "[g]ranting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, in the case of patents combining previously known elements, deprive prior inventions of their value or utility." *Id.* at 419. "In other words, obviousness exists when 'a finite, and in the context of the art, small or easily traversed number of options ... would convince an ordinarily skilled artisan of obviousness.' " *Purdue Pharma Products L.P. v. Par Pharmaceutical, Inc.*, 642 F.Supp.2d 329, 368 (D. Del 2009) (quoting *Ortho–McNeil Pharm., Inc. v. Mylan Labs.*, Inc., 520 F.3d 1358, 1364 (Fed. Cir. 2008)).

The Supreme Court in *KSR* rejected a rigid standard in favor of a more flexible obviousness standard. The Court held that a patent may be obvious in light of the combination of prior art if the combination was "obvious to try." *Id.* at 421. This more flexible standard expands the obviousness analysis beyond just "published articles and the explicit content of issued patents." *Id.* at 419. Other forces, including forces such as market demand, may also be examined to determine whether it would be obvious to combine more

than one known element. *Id.* In broad terms, "any need or problem known in the field of endeavor at the time of the invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. The Federal Circuit has noted that a finding of obviousness "does not require absolute predictability of success ... all that is required is a reasonable expectation of success." *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) (quoting *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988)); *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (same); *see also Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) ("[T]he expectation of success need only be reasonable, not absolute" nor "a guarantee.").

In conducting the obviousness analysis, the claimed invention must be viewed in light of the art that existed at the time the invention was made. *See* 35 U.S.C. § 103(a); *Uniroyal*, 837 F.2d at 1050–51. "The term 'prior art' as used in section 103 refers at least to the statutory material named in 35 U.S.C. § 102" that was available to a hypothetical person of skill in the art at the time the invention was made. *Riverwood Int'l Corp. v. R.A. Jones & Co., Inc.*, 324 F.3d 1346, 1354 (Fed. Cir. 2003). "To ascertain the scope of the prior art, a court examines the field of the inventor's endeavor and the particular problem with which the inventor was involved." *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir.1998) (citations and internal quotes omitted).

What a reference teaches is a question of fact. *In re Bell*, 991 F.2d 781, 784 (Fed. Cir. 1993). The Court should not "analyze each prior art reference in isolation without considering the prior arts' teaching as a whole in light of the creativity and common sense of a person of ordinary skill." *Duramed Pharms., Inc. v. Watson Labs., Inc.*, 2011 WL 1086573, at *4 (Fed.Cir. Mar.5, 2011). Even when all claim limitations are found in prior art references,

the fact-finder must determine what the prior art teaches, whether prior art teaches away from the claimed invention, and whether there was motivation to combine teachings from separate references. *See DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed. Cir. 2006). All teachings in the prior art must be considered in the obviousness determination, "including that which might lead away from the claimed invention." *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed.Cir.1988). "[A] reference must be considered as a whole, including the portions that argue against or teach away from the claimed invention." *Armament Sys. & Procedures, Inc. v. Monadnock Lifetime Prods., Inc.*, 1998 WL 537746, at *8 (Fed. Cir. Aug.7, 1998) (citing *Bausch & Lomb*, 796 F.2d at 448). "Where the prior art contains apparently conflicting teachings (*i.e.*, where some references teach the combination and others teach away from it) each reference must be considered for its power to suggest solutions to an artisan of ordinary skill[,] considering the degree to which one reference might accurately discredit another." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (citation and internal quotes omitted).

Importantly, courts have warned against improperly using hindsight in the obviousness analysis. It is impermissible to use "hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention." *Innogenetics, N.V. v. Abbott Laboratories*, 512 F.3d 1363, 1374 n. 3 (Fed. Cir. 2008); *see also KSR*, 550 U.S. at 421; *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999) ("Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field."), abrogated on

other grounds, *In re Gartside*, 203 F.3d 1305 (Fed. Cir. 2000). "A factfinder should be aware ... of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning." *KSR*, 550 U.S. at 421.

Obviousness is determined from the perspective of a hypothetical person of skill in the art ("POSA") at the time the invention was made. *See Bausch & Lomb, Inc. v. Barnes–Hind/Hydrocurve, Inc.*, 796 F.2d 443, 447–48 (Fed.Cir.1986). This hypothetical person

> is presumed to be aware of all the pertinent art. The actual inventor's skill is irrelevant to this inquiry, and this is for a very important reason. The statutory emphasis is on a person of ordinary skill. Inventors, as a class, according to the concepts underlying the Constitution and the statutes that have created the patent system, possess something—call it what you will—which sets them apart from the workers of ordinary skill, and one should not go about determining obviousness under § 103 by inquiring into what patentees (i.e., inventors) would have known or would likely have done, faced with the revelation of references.

Bausch & Lomb, 796 F.2d at 448. The reason that the obviousness analysis is conducted from the perspective of one skilled in the art "is to assure an appropriate perspective of the decisionmaker, and to focus on conditions as they existed when the invention was made." *Arkie Lures, Inc. v. Gene Larew Tackle, Inc.*, 119 F.3d 953, 956 (Fed. Cir. 1997). "Good ideas may well appear 'obvious' after they have been disclosed, despite having been previously unrecognized." *Id.* "Because patentability is assessed from the perspective of the hypothetical person of ordinary skill in the art, information regarding the subjective motivations of inventors is not material." *Merck Sharp & Dohme Pharms., SRL v. Teva Pharms. USA, Inc.*, 2009 WL 3153316, at *46 (D.N.J. Aug.19, 2009) (citations and internal quotes omitted); *see also KSR*, 550 U.S. at 419 ("In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls.").

A POSA may be defined according to several factors, including: "(1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 696 (Fed. Cir. 1983). The educational background of the inventors themselves may be a factor in determining the level of ordinary skill in the art, however, it is not conclusive. *See Bausch & Lomb*, 796 F.2d at 449–50.

The POSA may be a composite of different types of individuals. *See Medinol Ltd. v. Guidant Corp.*, 341 F.Supp.2d 301 (S.D.N.Y. 2004) (POSA was "an engineer working with a physician" or a "stent design team"); *Univ. of Rochester v. G.D. Searle & Co.*, 249 F.Supp.2d 216, 228 n. 6 (W.D.N.Y.2003) (POSA was "a team of scientists, with skills in medicinal chemistry, molecular biology, biochemistry, and pharmacology."). The POSA for a claimed method of treatment may include the skills of a clinician or medical professional. *See, e.g., Merck & Co., Inc. v. Teva Pharms*. USA, Inc., 347 F.3d 1367, 1371 (Fed. Cir. 2003) (POSA for a patented method of treating osteoporosis had a medical degree, experience treating patients, and knowledge of pharmacology); *Eli Lilly & Co. v. Teva Pharms. USA, Inc.*, 2004 WL 1724632, at *33 (S.D. Ind. July 29, 2004) (POSA for a patented method of using fluoxetine to treat premenstrual syndrome included a medical doctor—an OB/GYN, family practice physician, or psychiatrist—who regularly saw and treated patients suffering from PMS and was familiar with the prior art).

B. Person of Ordinary Skill in the Art

At trial, Defendants' expert Dr. Barnhart defined the relevant POSA as a physician with specialized training in gynecology, experience in research and development of oral

contraceptive regiments, and experience in clinical administration and evaluation of oral contraceptive regimens; or a Ph.D. with knowledge of pharmacological effects of contraceptive steroids and experience in research and development oral contraceptive regimens. Tr. 56:14-57:1. Plaintiff's expert Dr. Darney, on the other hand, offered a slightly different definition, defining a POSA as a physician with several years of experience prescribing oral contraceptives, or a person with an advanced degree in physiology, pharmacology, or pharmaceutical science who studied oral contraception specifically for years. Tr. 620:19–25. The key difference between the parties' definitions is whether experience in the development of oral contraceptive regiments is required. The Court, considering the appropriate standards as set forth above, concludes that it is not required and, therefore, adopts Plaintiff's definition of a POSA. The Court notes, however, that both Dr. Barnhart and Dr. Darney testified that their opinions would remain unchanged if even if the other's POSA definition were used, therefore the Court's conclusion does not alter the opinion of Defendants' expert in any way. *See* Tr. 57:24–58:3; 621:1–10.

C. Principal Prior Art References Relied Upon by Defendants

1. The '490 Patent

U.S. Patent No. 5,756,490 (the " '490 patent"), entitled Pharmaceutical Combination Preparation for Hormonal Contraception, discloses providing a combination of progestin and estrogen (preferably 15-25 μg EE) for 23 or 24 days, followed by the administration of estrogen-only for 4 to 10 days. Tr. 93:15-20 ; JTX 012. This is the primary prior art reference relied upon by Defendants.

2. The ’394 Patent

United States Patent No. 5,552, 394 (the “’394 patent”), entitled Low Dose Oral Contraceptives With Less Breakthrough Bleeding and Sustained Efficacy, discloses providing estrogen and progestin for 23–25 days, followed by four days of placebos. JTX-10.

3. The ’940 Patent

United States Patent No. 5,980,940 (the “’940” patent), entitled Pharmaceutical Combination Preparation for Hormonal Contraception, discloses providing a combination of a progestin and an estrogen for 23 or 24 days, followed by 2 or 1 days of placebo, followed by 4, 3 or 2 days of estrogen only. Tr. 61:5-23; 96:1-19; JTX 016.

D. Whether the ‘984 Patent is Obvious

As noted previously, to prevail on the defense of obviousness, Defendants are required to establish by clear and convincing evidence that “the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art.” 35 U.S.C. § 103(a). Thus, the Court must examine whether it would have been obvious for a POSA in April 2005 to combine prior art elements to create the contraceptive regimen of the ‘984 patent. For the reasons below, the Court finds that Defendants’ have not shown obviousness by clear and convincing evidence; rather, the evidence at trial showed that, as Plaintiffs contended, Defendants’ obvious analysis was based on hindsight.

1. Obviousness and the ‘940 Patent

Defendants’ obviousness defense relies in large part on the teachings of the ’940 patent, which was not before the examiner. The ’940 patent, which issued on November 9, 1999, describes a contraceptive in which “the first hormone component comprises 23 or 24

daily units and the second hormone comprises 4, 3, or 2 daily units, and between these two hormone components, 2 or 1 active ingredient-free daily units are present or 2 or 1 blank pill days are indicated." JTX-16, Abstract. The first hormone component is a combination of estrogen and progestin; the second component is estrogen only; placebo tablets are administered between these two hormone components. JTX-16, col. 5, ll.33-48; col 1, ll.21-31.

The '940 patent specifies a number of dosages for estrogen and progestin, as well as different ranges for the days of each phase of the administration scheme. JTX-16, at col. 4, l.18–col. 5, l.48. According to Dr. Darney, the '940 patent encompassed approximately 6.2 million potential oral contraceptive regimens. Tr. 816:17–817:3, 798:23–801:13; *see also* PTX-151, at 1; PTX-152, at 2. Although Defendants' expert Dr. Barnhart testified that a POSA would not view the patent as disclosing millions of combined oral contraceptive regimens because a POSA would understand that there are components in the patent that relate to the point of novelty, the Court nonetheless finds, crediting Dr. Darney's testimony, that the '940 patent discloses a very substantial number of potential oral contraceptive regimens.

The Court notes that in conducting its overall evaluation of the evidence, it has generally given weight to the opinions of Dr. Darney over Dr. Barnhart. The Court finds Dr. Barnhart's analysis to be driven in large part by hindsight. For example, as Plaintiff points out, Dr. Barnhart testified as to three general principles that a POSA would apply in developing an oral contraceptive regimen. He testified (1) that when looking to develop a new oral contraceptive, it is logical for a POSA to start with and modify a commercially successful regimen, Tr. 203:24–204:6; (2) that a POSA would have believed in the

importance of evidence-based medicine and in the primacy of data, and that when looking to develop a new oral contraceptive, it would be logical to start with a regimen that had already been proven to have efficacy and acceptable cycle control, Tr. 164:12–165:12; 204:4–204:6; and (3) that a POSA developing a new oral contraceptive regimen would want to "proceed one step at a time" because "in science, it is easier to determine the result of a specific change rather than to make a multiplicity of changes and attempt to determine the attribution of the results of each specific choice," Tr. 202:14–203:23.

However, in his testimony regarding Defendants' assertion that the '984 patent was obvious over the '940 patent, Dr. Barnhart pointed to nothing that showed any of these principles were followed along the allegedly obvious path form the '940 patent to claimed invention. First, Dr. Barnhart did not point to any commercially successful product, or any product for that matter, that resulted from the '940 patent. Tr.216:20-23; 812:16-18. Second, the '940 patent contains no data that demonstrates the efficacy or cycle control of any of the many regimens that the '940 patent encompasses. Tr. 216:17-19, 216:24 - 217:1. Finally, to arrive at, for example, the regimen of claim 6 of the '984 patent from the '940 patent, a POSA would have had to have made at least five changes, as follows: (1) select an ultra-low EE range of 5–15 µg, rather than the 15–25 µg EE range in the '940 patent; (2) deviate from the progestins listed in the '940 patent and choose NA; (3) deviate from the progestin dosages in the '940 patent and choose 1 mg; (4) change the order of administration in the '940 patent by reversing the order of the placebo and estrogen-only tablets; and (5) select the same EE dose for the combination and estrogen-only tablets. Tr. 216:13–221:18. Thus, it appears that Dr. Barnhart's obviousness opinion contradicts the very principles he states would have applied.

POSA Would Not Have Been Motivated

The evidence at trial also demonstrated a number of reasons why a POSA in April 2005 would not have been motivated to make the oral contraceptive regimen described in the '984 patent (5-15 µ EE combined with one milligram of NA), and nothing in the '940 patent alters this.

The '940 patent lists many progestins for potential use in an oral contraceptive JTX-16, col. 4, l.36−col. 5, l.7, but notes two progestins in particular: gestodene and levonorgestrel. JTX-16, col. 5, ll.22–24; *see also* Tr. 816:12–15. Gestodene and levonorgestrel were second- and third-generation progestins[3] that were well known for their potency and longer half-life. Tr. 648:1-653:15. The '940 patent does not mention NA, which was a less potent first generation progestin with a shorter half-life. JTX-16; Tr. 218:10–18; Tr. 648:1-653:15. A POSA would have had no reason to ignore the '940 patent's emphasis on gestodene and levonorgestrel, and instead to select NA.

Nothing in the '940 patent taught that 5–15 µg EE could be combined successfully with 1 mg NA. Tr. 815:11–18. While the '940 patent provides an EE range of 15–25 µg, it does not suggest anywhere that 15 µg EE, which is the only point of intersection between the ranges of the '940 patent and the asserted claims of the '984 patent, could be used successfully with NA. As discussed below, because the prior art taught against the use of NA with less than 20 µ of EE, a POSA would have believed that more estrogen would be required with NA, a weaker progestin with a shorter half-life .

[3] The progestins used in combination oral contraceptives are sometimes classified by "generation." The oldest progestins, known as "first generation" progestins, date back to the 1960s and include norethindrone and NA. Tr. 646:18–21, 615:16–24. "Second generation" progestins include norgestimate and levonorgestrel, while "third generation" progestins include desogestrel and gestodene. Tr. 646:22–647:6.

A POSA would have recognized that not all of the many regimens encompassed within the scope of the ’940 patent would be contraceptively effective and provide good cycle control with an acceptable side effect profile. Tr. 202:10−13. Indeed, the ’940 patent pointed out the difficulties experienced in lowering EE dose below 20 µg, reporting that the “risk of pregnancy is … high, especially in the case of intake errors below the 20 µg ethinylestradiol preparations.” JTX-16, col. 3, ll.36–39; *see also* JTX-12 (U.S. ‘490 patent), col. 3, ll.36–39 (same); Tr. 806:1–13. In light of the absence of data in the ’940 patent regarding the efficacy or cycle control of a 15 µg regimen, a POSA would not necessarily have been led to make an oral contraceptive combining 15 µg EE with 1 mg NA. Tr. 818:24–819:6; Tr. 216:17–19, 216:24–217:1; *see also* Tr. 164:12–165:12 (POSA would have believed in the “primacy of data”).

Additionally, data and prior art outside the ‘940 patent suggested that a sub-20 µ EE dose paired with 1 mg NA would not work to make an effective oral contraceptive with acceptable cycle control. First, the prior art taught that problems with efficacy and cycle control could result when lowering EE to or below 20 µ. Second, the prior art taught generally that NA was a weak progestin with a short half-life, and that 1 mg with 20 µ of EE raised concerns regarding efficacy and poor cycle control. Third, the prior art taught that a more potent progestin should be used if EE was to be lowered below 20 µ. Each of these are discussed in turn below.

<u>POSA Expectations - Lowering EE To or Below 20 µ</u>

At some point after the introduction of the first oral contraceptive in 1961, scientists discovered that high estrogen doses were associated with a high risk two serious conditions, deep vein thrombosis and pulmonary embolism. This discovery led to a significant reduction

in estrogen dose used in such contraceptives. Tr. 639:25–641:8; 672:12–674:13. By the next decade, researchers had lowered estrogen to a conventional daily dose of 30–35 µg EE. Tr. 679:1–6. Studies showed that oral contraceptives at this dose were quite safe. Tr. 149:13–150:3, 237:17–238:1; 705:17–706:6, 812:16–813:19.

In 1973, Loestrin 1/20 was launched, an oral contraceptive which paired 20 µg EE with 1 mg NA. Tr. 671:5–19; PTX-135. However, as of 2005, in the more than 30 years that followed the introduction of Loestrin 1/20, no oral contraceptive with less than 20 µg EE was introduced in the United States. Tr. 671:25–672:8; PTX-135. Evidence showed at least two reasons why further reductions in EE did not occur.

First, there was widespread recognition that lowering estrogen dose further could threaten contraceptive efficacy. Tr. 709:23–710:8, 697:4–703:14. The prior art taught that women using oral contraceptives with 20 µg EE had larger ovarian follicles than women using oral contraceptives with higher EE doses, which signaled that such women would be more likely to ovulate and become pregnant. Tr. 697:16–702:9; DTX-507 at 242 ("The present data suggest that a decrease in the EE content as seen in the 20 µ EE containing [combined oral contraceptive] results primarily in larger follicle during the pill-free interval. Because follicles maintain the potential to ovulate, contraceptive efficiency in [combined oral contraceptive] should include the prevention of dominant follicles."); DTX-477 at 303 ("It can be concluded that ethinyl estradiol dose in an oral contraceptive has a significant effect on follicular ovarian activity, and that reducing the dose to 20 µ is associated with a significant increase in follicle size."); *see also* JTX-16 at col. 2, ll.61–67; PTX-82A at 39–40. Consequently, a POSA would have expected that lowering EE even further to less than 20 µ would have increased follicle size even further and put women at a greater risk of unintended

pregnancy. It followed that no oral contraceptives marketed in the United States as of 2005 used less than 20 µ in the combination phase. Tr. 702:3–706:18; 709:23–710:8; *see also* PTX-83 at 39 ("We are probably at or very near the lowest dose levels that can be achieved without sacrificing efficacy."); Tr. 702:3–22.

Second, there was widespread recognition that as estrogen doses declined, cycle control problems increased, which would have counseled against lowering estrogen below the daily dose of 20 µg EE used in Loestrin 1/20. Tr. 673:9–679:16; PTX-48, at 16S; PTX-21, at 163; PTX-99; PTX-1, at 837. Cycle control refers to the degree to which an oral contraceptive is able to mimic the normal and expected menstrual cycle. Tr. 673:9–13. The parties' experts agreed that a POSA in 2005 would have understood that estrogen is critical to maintaining cycle control, and that cycle control greatly affects whether a woman will continue with an oral contraceptive. Tr. 151:14–153:19; Tr. 687:14–689:23; PTX-82a at 40. A number of prior art references stated that as the estrogen dose decreased, cycle control became worse. PTX-99 at 3 ("However, when OC formulations with the same progestin component are compared, the lower the dose of estrogen, the more diminished is the cycle control.") ; PTX-21 at 163 ("The frequency of BTB and spotting has been shown to increase as the estrogen dose decreases."); PTX-1, at 837 ("A difference was demonstrated … was the less effective cycle control with the 150/20 combination …")

Problems with cycle control include breakthrough bleeding and spotting that occurs during the active period of hormone administration. Tr. 673:9–13. Such bleeding can affect not only whether a woman continues taking an oral contraceptive, but also the quality of her life. Tr. 688:9–689:23; see also Tr. 978:17–979:7; PTX-82a at 94. As such, cycle control would have been an important consideration to a POSA. Tr. 151:20–152:25, 153:16–19

(patients complain about unscheduled bleeding while on oral contraceptives, women find unscheduled bleeding disturbing for many reasons, it is one of the more common reasons women discontinue oral contraceptives); Tr. 153:4–15 (women and men avoid sexual relations during vaginal spotting, and women may discontinue a contraceptive method because of its effect on sexual enjoyment).

In light of the above considerations, a POSA seeking to reduce estrogen dose in a new contraceptive regimen would have balanced the potential benefit from a safety standpoint with the expected loss of efficacy and cycle control, and likely would have concluded that these factors weighed against lowering estrogen dose below 20 µ. Tr. 812:19–813:24, 705:17–706:18, 709:23–710:8

Prior Art Teaching re: Use of NA with EE Less than 20 µ

Even if a POSA would have sought to lower estrogen dose to below 20 µ EE in a new oral contraceptive, that person would likely not have used NA as the progestin. There are a number of considerations that would have informed a POSA as to which progestin to use, and these considerations lead away from NA.

There are a number of different progestins that have been developed over the years. Tr. 645:15–647:6. They have different molecular structures and properties, are not interchangeable. Tr. 645:15–653:15; 667:18–668:10. Significantly, the different progestins have different potencies, and weaker or less potent progestins bind to progesterone receptors with less strength than the more potent progestins. Tr. 647:7-25. Relevant prior art taught that more potent progestins had certain advantages over less potent ones in terms of contraceptive efficiency, as they were better at suppressing ovarian activity and at making cervical mucus less sperm-penetrable, and result in less endometrial bleeding. Tr. 650:21-

651:25, 652:1-3. Prior art further taught that first generation progestins norethindrone and NA were less potent than second generation pro-gestins levonorgestrel and norgestimate, and third generation progestins desogestrel and gestodene. Tr. 648:3–7; 648:25–650:20; PTX-87 at 222.

Another consideration regarding progestin in an oral contraceptive is half-life. This refers to the length of time that it takes for that progestin to reach half of its original concentration after reaching its peak concentration in the body. Tr. 652:14–16. The prior art recognized that the second and third generation progestins have longer half-lives than first generation progestins. Tr. 653:4–16, 657:14–20. For example, the first generation progestin norethindrone has a half-life of about eight hours, whereas gestodene, a third generation progestin, has a half-life of about 14 hours. Tr. 653:10–15; 657:14–20.

Progestin half-life has implications with respect to efficacy and cycle control. Progestins with longer half-lives have an advantage in terms of contraceptive efficacy because the progestin remains in the woman's body longer to be contraceptively effective. Tr. 652:17–653:15; 655:10–656:14. Consequently, with a longer half-life it is not as important for women to take the pill exactly on time every day; a woman can take her pill several hours late and still have an adequate concentration of drug to inhibit ovulation or keep the cervical mucus viscous. Tr. 655:10–656:14.

With respect to cycle control, if a woman is taking an oral contraceptive containing a progestin that has a shorter half-life, and forgets to take it at the same time she usually takes it, or forgets to take it entirely, progestin withdrawal will begin and the woman will begin her withdrawal bleed. Tr. 656:15–657:24. Progestins with longer half-lives avoid this problem. Tr. 656:15–657:24.

Relevant prior art recognized that the weaker progestin NA, with its shorter half-life, resulted in poor cycle control when NA was used in low-dose oral contraceptives. PTX-112, col. 3, ll.17–37; 712:6–713:25 (Formulations using norethindrone and NA "were associated with breakthrough bleeding and unpredictable uterine bleeding in 40 to 50% of the cases" and, as a result, "there acceptance has been minimal."). Prior art also recognized that that efforts to reduce estrogen below 30 µg with NA were not successful. PTX-78, at 2 ("[T]he first 20 mcg or 15 mcg EE pills were rapidly abandoned due to inadequate contraceptive efficacy and/or poor cycle control resulting above all in unacceptable irregular bleeding."); Tr. 715:13–717:24

The performance of Loestrin 1/20, an oral contraceptive that used 1 mg NA in combination with 20 µg EE, would have informed a POSA with respect to using NA in combination with low doses of estrogen in an oral contraceptive. Clinical experience prior to 2005 showed that Loestrin 1/20 was associated with a high rate of unintended pregnancies as well as poor cycle control. Tr. 679:10–18; 690:3–17; 693:22–694:13. It was reported that Loestrin 1/20 "was shown to be significantly less acceptable and effective" than a 30 µg EE oral contraceptive. PTX-97 at 238; Tr. 690:18–691:20; *see also* PTX-52 at 71–72; Tr. 691:22–693:21 (studies showed a relatively high incidence of unintended pregnancies and a high rate of irregular bleeding with Loestrin 1/20 regimen). It was also reported that Loestrin 1/20 exhibited "poor" cycle control, with a high rate of unscheduled bleeding and discontinuation rates due to such bleeding several times higher than a 30 µg EE oral contraceptive. Tr. 679:20–681:15; PTX-10 at 327; 328, Table II; *see also* PTX-93, at 56–57; (Because unscheduled breakthrough bleeding with Loestrin 1/20 "is almost universal, this pill has never been very popular."); Tr. 684:19–687:19.

Thus, it is not surprising that in the 20 years following Loestrin 1/20's introduction, not a single new oral contraceptive with an estrogen dose as low as 20 µg EE was introduced in the United States. Rather, all new regimens used at least 30 µg EE. Tr. 703:15–706:18. A POSA would have understood that this reflected, and was attributable to, the high bleeding rates and questionable efficacy exhibited by Loestrin 1/20. Tr. 705:22–706:18.

Even the manufacturer of Loestrin 1/20 recognized that its performance was problematic and attempted to modify Loestrin 1/20 and improve its poor cycle control by creating a regimen that added estrogen to sixteen of the twenty-one combination tablets. Tr. 686:20–687:19. Estrostep was approved in 1996, and was the only new regimen containing NA introduced in the United States in the twenty years leading up to the April 2005 invention date. Tr. 162:25–163:23; Tr. 663:20–23; PTX-135. Significantly, Estrostep increased -- not decreased -- the estrogen dose to address the efficacy and cycle control problems of Loestrin 1/20. Thus, Estrostep taught a POSA that more than 20 µg EE should be used with 1 mg NA, not that an acceptable oral contraceptive could be designed with even less estrogen than was used in Loestrin 1/20.

The prior art may be said to teach away, when, as here, "a person of ordinary skill, upon reading the reference, would be … led in a direction divergent from the path that was taken by the applicant." *Tec Air, Inc. v. Denso Mfg. Mich., Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999). The Court finds that the Estrostep regimen in addition to the other prior art above, taught away from the claimed invention of the '984 patent.

Newer Progestins

In light of the considerations and prior art discussed above, a POSA would not have sought to lower lower EE below 20 µg EE with NA. Rather, if a POSA had tried to make a

combination oral contraceptive with less than 20 µg EE in 2005, the prior art taught use of a newer, more potent progestin with a long half-life rather than the less potent, first-generation progestin such as NA. Tr. 714:2–21; 721:8–723:18; *see also* PTX-112 ('315 patent taught that a more potent progestin was required when reducing EE); Tr. 717:4-8, 15-21; PTX-78 at 2 (prior art explaining that efforts to lower estrogen dose below 30 µg EE with NA had failed, but the appearance of newer progestins such as desogestrel may open development possibilities).

Indeed, this is confirmed by the fact that as of April 2005, there was only one combination oral contraceptive available anywhere that contained an estrogen dose less than 20 µ. Minesse was a regimen available in Europe that combined 12 µ EE with gestodene, a potent, third-generation progestin. Tr. 710:13–711:15; 721:8–723:18. The art at the time attributed the efficacy of Minesse to its use of gestodone. PTX-32 at 306 (Fruzzetti) ("Until now the lowest available dose was 20 µg," but "[t]he availability of a potent progestin, such as gestodene, makes possible a further decrease in the estrogen dose to 15 µg without compromising the contraceptive efficacy of the preparation."); PTX-7 (Bianchi) at 109 (explaining that gestodene appeared to offer better cycle control); *see also* Tr. Tr. 721:10–723:7, 723:19–725:1.

Consequently, if a skilled artisan in 2005 were attempting to reduce EE below 20 µ, he or she likely would have used one of the new progestins, not NA or norethindrone. Nothing in the '940 patent would change this, particularly in light of the fact that the '940 patent emphasized gestodene.

Nor does the Court find there to be sufficient evidence to support the contention that a "pill scare" would have led a skilled artisan to disregard the preference in the prior art

discussed above for the newer progestins. Tr. 121:3-11. Dr. Barnhart testified that a "pill scare" arose in the mid-to-late 90s following the publication of several clinical reports that concluded that combined oral contraceptives using third generation progestins were associated with a higher risk of a serious side effect, specifically, venous thromboembolism. Tr. 121:3-11. However, Dr. Barnhart's testimony did not examine the extent of the continued vitality of the "scare" at the relevant time period--April 2005, nearly a decade after the controversy began. *See* Tr. 726:6-25. Indeed, new regimens using gestodene, desogestrel, and norgestimate were developed and launched after the "pill scare" controversy emerged: Ortho Tri-Cyclen Lo (norgestimate), Cyclessa (desogestrel), and Mircette (desogestrel) in the United States, (PTX-135), and Minesse (gestodene) in Europe. Tr. 731:14–20; 239:25–240:14.

2. Order of Administration

The '984 patent requires a particular 24/2/2 administration schedule: tablets containing a combination of EE and NA are administered for 24 days, followed by two days of EE-only tablets, followed by two days of placebo tablets. JTX-1. The '940 patent teaches a different 24/2/2 schedule, with the placebo tablets preceding the EE-only tablets. The Court finds that the '940 patent would not have led the skilled artisan to use the order of adminstration claimed in the '984 patent.

Contrary to claims by Defendants and the opinion of Dr. Barnhart, the '940 patent does attribute benefits to its order of administration, noting that the order of the regimen "ensures withdrawal bleeding and produces in the subsequent administration cycle a reduced rate of intracyclic menstrual bleeding compared with conventional, low-dosed preparations." JTX-16, col 4, ll.28-35. According to Dr. Darney, a POSA would have believed that providing estrogen-only tablets immediately before the combination tablets would confer

advantages both in terms of cycle control and efficacy, and that such a person would have seen no reason to change this order of administration. Tr. 821:4–822:15, 825:5–830:2.

Other prior art recognized that providing estrogen-only tablets immediately before combination tablets allowed the estrogen to "prime" progesterone receptors, which would allow the subsequently administered progestin to bind more readily to progesterone receptors in the lining of the uterus, and result in a better bleeding pattern. Tr. 825:5–826:25. For example, the '843 patent explained that "[estrogen] stimulate[s] progesterone receptor sites. By stimulation of progesterone receptors early in the menstrual cycle, estrogen administration allows a reduction in the incidence of intermenstrual bleeding. That is, breakthrough bleeding and spotting are minimized ... ." JTX-15, col. 4, ll.3–8; Tr. 851:9–852:20, 825:5–826:19. This concept of progestin priming was employed by the '843 patent employed by providing estrogen-only tablets immediately before combination tablets, just as the '940 patent did. JTX-15, col. 4, ll.3–8; Tr. 851:9–852:20, 825:5–826:19.

The regimen of the contraceptive Mircette, an embodiment of the '843 patent and, as of the relevant time in 2005, the only marketed oral contraceptive that used estrogen-only tablets (PTX-135), also employed those tablets after the placebos, and immediately before the next cycle's combination tablets. Tr. 825:5–828:21. By 2005, there had been seven years of clinical experience with Mircette, PTX-135, and the prior art reported that its placement of estrogen-only tablets immediately before the combination tablets was successful. PTX-50 at S24; Tr. 827:3–828:21 ("The results of this study appear to validate the rationale for the administration of 10 μg ethinyl estradiol during the last 5 days of the 7–day nominally hormone-free interval of the Mircette regimen."). Notably, nowhere did the prior art teach that one could achieve the same effect on progesterone receptors if one reversed the order of

the estrogen-only and placebo tablets, *e.g.*, by including a placebo period immediately before the combination tablets and after the unopposed estrogen tablets. Tr. 828:15–829:24, 852:11–19. In light of these teachings, a POSA would have understood that if one were going to use estrogen-only tablets in an oral contraceptive, it was important to administer them immediately before the combination tablets. Thus, to the extent that Dr. Barnhart testified that switching the order of estrogen-only and placebo pills days would not make a difference in efficacy or cycle control, the Court finds the weight of the evidence to be to the contrary.

The Court similarly finds little support for the argument that a POSA would have been motivated to reverse the order of the tablets in the '940 patent in order to increase the incidence of amenorrhea, *i.e.*, the absence of withdrawal bleeding during administration of placebo pills. Tr. 97:10–100:13; Tr. 885:12–15. According to Dr. Barnhart, amenorrhea was a "good side effect." Tr. 99:10–102:7. However, the Court finds the credible evidence to be otherwise, and concludes that amenorrhea was generally an unwanted side effect. Tr. 837:22–24, 839:18–25. Not having a menstrual period is a sign of pregnancy -- the very condition use of a contraceptive is designed to avoid -- so amenorrhea raises the concern that the contraceptive is not working. Tr. 837:22–838:11. Partly for this reason, oral contraceptives have been designed to allow for periodic withdrawal bleeding. Tr. 838:6–11. Concerning amenorrhea, Clinical Guide to Contraception (Darney, PTX-83) stated that

> [t]he major problem with amenorrhea while on oral contraception is the anxiety produced in both patient and clinician because the lack of bleeding may be a sign of pregnancy. The patient is anxious because of the uncertainty regarding pregnancy, and the clinician is anxious because of the medicolegal concerns stemming from the old studies, which indicated an increased congenital abnormalities among the offspring of women who inadvertently used oral contraception in early pregnancy ... .

> Amenorrhea is a difficult management problem. A pregnancy test allows reliable assessment for pregnancy even at this early stage. However routine, repeated use of such testing is expensive and annoying and may lead to discontinuation of oral contraception ... .

PTX-83, at 99.

Furthermore, as the ’940 patent itself recognized, lower incidence of amenorrhea results in better compliance. Tr. 838:14–839:10; JTX-16, col. 6, ll.33–39. Women who experience amenorrhea on oral contraceptives, mistakenly thinking they may be pregnant, sometimes discontinue oral contraceptives—which can itself result in unintended pregnancy. Tr. 838:14–839:10. A POSA would have wanted to avoid such results, and therefore would not have wanted to increase the incidence of amenorrhea. Tr. 838:14–839:10. 205. Thus, the Court finds that Defendants have not shown that a desire to increase amenorrhea would have motivated a skilled artisan to reverse the order of placebo and estrogen-only tablets in the ’940 patent.

The Court is also not persuaded by testimony that United States Patent No. 6,133,251 (“the ’251 patent”) would have taught a POSA to reverse the order of placebo and estrogen-only tablets in the ’940 patent to arrive at the 24/2/2 scheme claimed by the ’984 patent. Tr. 88:17–89:19. Rather, the Court concludes that a POSA seeking to make an oral contraceptive with 5–15 µg EE and NA would not even have looked to the ’251 patent or considered it relevant because it was a “fundamentally different” regimen. Tr. 841:10–843:18. First, the ’251 patent was “based on natural estrogens,” requiring that at least one natural estrogen be included in the regimen. The ’984 patent uses synthetic estrogen. JTX-13, col. 1, ll.6–7, col. 3, ll.22–33; Tr. 842:10–23. Second, the ’251 patent facilitated the use of “extremely high estrogen daily dosage,” JTX-13, col. 4, ll.3–4., while the ’984 patent, which employs ultra-

low doses of estrogen. Finally, unlike the ’984 patent, which claims the use of NA, the ’251 patent does not even mention NA. *See* JTX-13. Thus, a POSA would not have looked to the ‘251 patent for guidance when choosing an administration scheme to use with a sub-20 µg EE regimen that employed NA. Tr. 843:8–18.

Similarly, the evidence does not establish that the ‘490 patent, which is closely related to the ‘940 patent, would have lead a POSA to the claimed order of administration. *See* Tr. 797:21-811:11. The ‘490 patent provides for 24 days of combination tablets, followed by 4 days of unopposed estrogen. JTX-12. It does not provide for a placebo and, in fact, provides estrogen-only tablets immediately prior to the combination tablets. The ‘490 patent, therefore, would no lead a POSA to the claimed order of administration.

2. Other References and Obviousness

Loestrin 24 Fe

Prior April 2005, Warner proceeded with the development of a 24/4 combination oral contraceptive regimen, Loestrin 24 Fe (“Loestrin 24”), which uses 24 days of combination pills containing 20 µ EE and 1 mg NA. Tr. 126:2-11. The Loestrin 24 product exemplifies Warner’s ’394 patent. Tr. 899:13-15; 937:25-938:2. According to Dr. Barnhart, a POSA in April 2005 would have been aware that this regimen was in development. Tr. 126:2-18. The NDA for Loestrin 24 was submitted to the FDA on April 15, 2005, and approved by the FDA on February 17, 2006. Thus, it was no later than April 15, 2005 that the Phase III clinical trials would have been completed; trials that tested the regimen on approximately 1,000 study participants. Tr. 131:20-132:19. The informed consent form disclosed the Loestrin 24 regimen—specifically that the same oral contraceptive containing 1 mg NA and 20 µg EE is administered for 24 days of a 28–day cycle. DTX-822B, WC_LP 0008587–WC_LP

0008588; Tr. 135:14–19. The informed consent form also provided a "notification option" allowing the study participant, among other options, to check a box stating "I want the study doctor to inform my primary care physician/specialist of my participation in this study." DTX-822B, WC_LP 0008593, Tr. 135:24–136:1. The participants had no duty of confidentiality with regard to the consent form. Tr. 135:20 – 136:8.

Based on the contents of the informed consent form, Dr. Barnhart testified that the information disclosed on the informed consent form was "clearly disseminated information … ." Tr. 135:14–136:8. The Court agrees with Plaintiff, however, that there was no evidence that dissemination of the regimen was actually made or that any participants' primary care physicians were actually informed of their patients' participation. Defendants appear to rely upon simply the existence and use of the informed consent form itself as evidence that knowledge of the development of Loestrin 24 was prior art. However, lacking clear and convincing evidence of actual dissemination, the Court concludes that knowledge of the development of Loestrin 24 is not prior art. *See Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1576 (Fed. Cir. 1996) (in a challenge to the validity of a patent, issues regarding the status of prior art must be shown by clear and convincing evidence).

<u>'394 patent</u>

The '394 patent discloses a regimen providing estrogen and progestin for 23–25 days, preferably for 24 days, followed by four days of no combination tablet administration. JTX-10 at col. 3, ll. 35–48. It discloses broad ranges of potential doses: estrogen doses range from the equivalent of l−35 µg EE JTX-10, at col. 3, l. 42; Tr. 200:19–201:9, and progestin doses range from the equivalent of 0.025 to 10 mg NA, the preferred progestin, *id.* at col. 3, l. 42–43; Tr. 201:10–17. The weight ratio of estrogen to progestin must be at least 1:45, and

preferably at least 1:50. JTX-10 at col. 3, ll.37–67. The patent states no preference for a particular EE or NA dose, but does state a preference for a particular range of NA doses: 0.5−1.5 mg. JTX-10, at col. 3, ll. 66–67. A POSA would have understood that not all regimens encompassed by these ranges of the '394 patent would have been contraceptively effective. Tr. 200:19−202:13. Further, as of 2005, there were no commercial embodiments of the '394 patent. Tr. 199:22−200:1. Although Defendants point to the '394 patent to support their contention that a 1 mg dose of NA was commonly used in the prior art, the Court finds no evidence that, based on the '394 patent, a POSA would have been motivated to make the claimed invention, or led a POSA to combine 1 mg NA with 5-15 μ EE.

3. Secondary Considerations - Indicia of Nonobviousness

The Federal Circuit has recognized that

> Objective indicia of nonobviousness play a critical role in the obviousness analysis. They are "not just a cumulative or confirmatory part of the obviousness calculus but constitute[ ] independent evidence of nonobviousness." *Ortho–McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008). … Objective indicia "can be the most probative evidence of nonobviousness in the record, and enables the court to avert the trap of hindsight." *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed.Cir.2010) (internal quotation marks omitted).

Leo Pharmaceutical Products, Ltd. v. Rea, 726 F.3d 1346, 1358 (Fed Cir. 2013). Here, the Court finds certain secondary considerations, in conjunction with the findings above, support a conclusion of nonobviousness.

Unexpected results are useful to show the "improved properties provided by the claimed compositions are much greater than would have been predicted." *Id.* Evidence at trial showed that the Pearl Index (a numerical representation of the efficacy of a combined oral contraceptive) of Lo Loestrin is not statistically significantly different than that of

Loestrin 24, which would be unexpected given the fact that Loestrin 24 has twice as much EE in the daily combination formulation. Tr. 502:20–514:23; PTX-146; PTX-233. Plaintiff's statistical expert Dr. Thisted conducted several analyses comparing the Pearl Index for Lo Loestrin to that of Loestrin 24. In all such comparisons, the difference in the Pearl Indices was not statistically significant. Tr. 511:7–514:23; PTX-146. The comparison between these two regimens is relevant to the analysis because Loestrin 24 is a commercial embodiment of the prior art '394 patent, and there are no commercial embodiments of the '940 or '490 patents against which to compare efficacy.

Another relevant factor as to unexpected results as well as other secondary considerations is Lo Loestrin's FDA approval. *See Leo Pharmaceutical Products*, 726 F.3d at 1358 ("While FDA approval is not determinative of nonobviousness, it can be relevant in evaluating the objective indicia of nonobviousness.") (citing *Knoll Pharm. Co., Inc. v. Teva. Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004). As Dr. Darney credibly testified, a POSA would not have expected the Lo Loestrin regimen to be sufficiently contraceptively effective to obtain FDA approval because of its low EE dose and use of a weak progestin, NA. Tr. 868:8–14, 869:15–970:18. Indeed, some in the industry were skeptical of the regimen's efficacy and cycle control. *See, e.g.*, Tr. 617:6-18; 983:12-20. But Lo Loestrin was approved as safe and effective by the FDA. PTX-233; Tr. 868:23–869:11. In the more than 30 years between the introduction of Loestrin 1/20 and 2005, no one received FDA approval for a sub-20 µg combination oral contraceptive. Tr. 671:25–672:8; PTX-135.

Finally, evidence showed that Lo Loestrin has enjoyed commercial success and fills an unmet need. Dr. Kagan, a practicing clinician who frequently prescribes oral contraceptives, testified that Lo Loestrin "really fills a niche for patients" and that it "is especially well-suited

for those women who could not use a combination birth control pill prior to this time." Tr. 989:14–990:9. Specifically, these are women who could not use combination oral contraceptives because of side effects related to the EE dose, such as nausea, breast tenderness, and headaches. Tr. 972:20–973:4, 987:2–990:9.

The oral contraceptive market is a highly competitive market. Tr. 325:9–326:24. There are well over 100 individual oral contraceptive products within this market and 40 distinct oral contraceptive regimens. *Id.* Lo Loestrin competes with both low-cost generic products as well as branded regimens promoted to physicians, including several new regimens launched at or around that same time as Lo Loestrin. Tr. 327:20–328:19. In this competitive environment, there were over 3 million prescriptions for Lo Loestrin from its launch in January 2011 through January 2013.[4] Tr. 329:10–330:20; PTX-168.

Lo Loestrin total prescriptions and new prescriptions increased steadily from the time of its launch. Tr. 331:22–332:17; PTX-168; PTX-162. Lo Loestrin sales revenue also increased steadily and significantly since its launch—over $250 million in net sales in the first 27 months since launch, and were on pace to be $250 million or more in 2013. Tr. 334:14–336:9; PTX-220; PTX-22; *see also* Tr. 336:25–337:9. Overall, Lo Loestrin sales and prescriptions exceeded Warner Chilcott's pre-launch projections by a substantial margin. Tr. 337:10–339:1.

Lo Loestrin's market share has been significant and continues to increase. Tr. 339:7–341:8; PTX-162; PTX-168. As of March 2013, Lo Loestrin had become one of the top 10 oral contraceptive regimens. Tr. 340:19–341:1 Sims. Lo Loestrin's market share

[4] As reported by IMS, a third-party service that reports on sales and prescriptions of pharmaceutical products. PTX-168

significantly exceeded that of four other new oral contraceptive regimens launched at around the same time—Beyaz, Natazia, Generess, and Safyral. Tr. 341:23–344:6; PTX-179.

Lo Loestrin's success is not necessarily attributable solely to marketing efforts and expenditures. Although Warner Chilcott has marketed Lo Loestrin to physicians, marketing of new oral contraceptive regimens is common in the industry; indeed, physicians will not write prescriptions for products of which they are unaware. Tr. 348:12–349:21; Tr. 982:4–15. Generally speaking, the purpose of marketing a new regimen to physicians is to educate physicians about the features and the benefits of the product. Tr. 346:14–348:8. Moreover, Warner Chilcott's marketing expenditures for the launch of Lo Loestrin were consistent with prior launches. Tr. 350:24–351:12. Warner Chilcott spent less on per-prescription and per-dollar sales basis than did other companies launching oral contraceptives in the same timeframe. Tr. 350:18–23.

Nor were the increasing sales necessarily attributable to pricing considerations. Lo Loestrin has achieved the aforementioned sales volume and market share despite (i) being priced at a premium to certain generic oral contraceptives; and (ii) being priced similarly—both in terms of wholesale pricing and in terms of formulary co-pays—to other branded products, indicating that Lo Loestrin's superior performance is not due to the pricing of the product, and but rather to the patented features of the regimen. Tr. 352:12–353:15.

In sum, the Court finds that the above secondary considerations support a finding that the '984 was not obvious over the prior art.

IV. CONCLUSION

For the reasons set forth above, the Court finds in favor of Plaintiff regarding Defendants' obviousness defenses, and judgment on that issue shall be entered accordingly.

The Defendants in these matters having stipulated to infringement, the Court shall enter judgment in favor of Plaintiff with respect to infringement as well.

/s/ JOEL A. PISANO
United States District Judge

Dated: January 17, 2014